DETAILED ACTION

Claims 1-12 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of arthritis, does not reasonably provide enablement for a pharmaceutical composition which is a regulator of a chemokine/chemokine receptor; or a method for **prevention** and/or treatment for inflammatory diseases, immunologic diseases, human immunodeficiency virus, etc. (the diseases recited in claim 11); or a method for antagonizing CCR5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the

claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims 9-10 are drawn to 'composition which is a regulator of chemokine/chemokine receptor or CCR5'. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

Claim 9 recites "composition which is a **regulator** of chemokine/chemokine receptor" and it is generally known that the term "regulation" encompasses antagonism, partial antagonism, agonism and partial agonism. However, the compounds were not shown to have all these properties. The specification only provides test data related to measuring antagonism of CCR5 and there is no disclosure, how one of ordinary skill in the art can extrapolate this data to find the 'chemokine regulation' activity of the compounds. For example, it is revolutionary for a compound to be effective as an antagonist and partial agonist/antagonist. The specification did not provide any competent tests or data to establish that the compounds have the claimed 'chemokine receptor regulating activity'. Havlioglu et al. (Journal of Neurovirology 2002) provide that "Chemokines are classified into several families according to their structural features" (page 486); "Although some viral-derived chemokine inhibitors have been reported, very little is known about endogenously produced chemokine inhibitors" (page 487); and conclude that "The studies on the interplay between chemokine pathways and other signal transduction pathways are only at the beginning. Mechanisms underlying the complex

regulation of chemokine signaling inside and outside the nervous system await further investigation with combined molecular, biochemical and functional approaches" (page 489). This establishes the uncertainties and the level of unpredictability in the relevant state of the art and therefore, one of ordinary skill in the art would be required to go through undue experimentation to find the regulating activity of the compounds.

The instant claim 12 is drawn to 'a method for antagonizing CCR5' and claim 11 is drawn to 'a method of treating inflammatory diseases, immunologic diseases, HIV, etc.'. The instant claims appear to be 'reach through' claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The instant claims recites method of treatment of various disorders and the specification fails to enable one skilled in the art for the recited use. The use disclosed in the specification is as therapeutic agents for the treatment of diseases listed in page 31, which includes various inflammatory diseases, autoimmune diseases, etc. First, the claims cover 'diseases' having diverse mechanisms and/or involving various organs and parts of a human body and therefore, the treatment recited in the claims is extremely broad. Further, there is no description regarding how to identify the subject 'in need of such treatment' of these assorted diseases. Test procedures for measuring the activity of the compounds in terms of antagonism of CCR5 is provided on pages 27-31, however, there is nothing in the disclosure regarding how this *in vitro* assay correlates to the treatment of the disorders of the instant claims. The data provided in

insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the compounds. The area of receptor interactions is highly structure specific and unpredictable. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of the treatment is identified and further, how all types of disorders of the claims having diverse etiologies are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the inhibitory data provided is insufficient for one of ordinary skill in the art in order to extrapolate to all types of disorders of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Enablement for the scope of "treatment of inflammatory disorders" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no,

and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name, given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is

by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammatory disorders. It establishes that it is not reasonable to any agent to be able to treat inflammatory disorders generally.

The instant claims recite 'a method for prevention and/or treatment of allergic diseases'. The number and complexity of allergenic triggers rise with each year that passes, the incidence of allergic diseases rises, and diseases like eczema have now reached epidemic proportions with no end in sight. Doctors and researchers struggle to find an effective therapeutic remedy, but so far have achieved only palliative remedies. Allergic reactions or diseases may involve any part of the body; the most frequently involved are the nose and chest with resultant symptoms of hay fever, rhinitis or asthma, respectively. The skin and eyes also commonly show allergic symptoms. Anaphylactic shock is a severe allergy, which affects many organs at the same time causing a rapid decrease in blood pressure, fainting and, occasionally, death. Allergies come in a variety of forms and vary in severity from mildly bothersome to life-threatening and there is no single method of treatment, which is known to be effective against all types of allergies.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'.

The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating or preventing' effect of a 'disease' solely based on the *in vitro* MCP-1 antagonizing activity disclosed for the compounds.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The scope of the method claim 11 is not adequately enabled solely based on chemokine receptor activity provided in the specification. The instant claims are drawn to 'a method for **prevention**' of diseases such as inflammatory diseases, HIV infection, etc., and therefore, the instant claim language embraces disorders not only for the treatment, but for "prevention" which is not remotely enabled. The instant compounds are disclosed have antagonism CCR5 binding activity and it is recited that the instant compounds are useful in the "prevention" of inflammatory disease, HIV infection, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. The specification does not provide any assay or test procedure, which relates to the therapeutic or preventive activity recited in the instant claims. Thus, it is inconceivable as to how the claimed compounds can not only treat but

also "prevent" a myriad of diseases with different etiologies. For example, a viral disease such as HIV infection has been known to be treated with a nucleoside analog or a protease inhibitor to disrupt the production of viral protein or DNA. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating a disease or condition in which regulation of chemokine receptor activity is beneficial, which includes diseases such as inflammatory diseases, immunologic diseases, etc.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat all types of diseases embraced by the instant claims.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders cited, etc. nor there are doses given for the treatment of the disorders recited. The specification provides test procedures (see pages 27-31) to test the compounds *in vitro* and indicates that the compounds of the invention have activity in the antagonism of CCR5. However, no *in vivo* test procedures or data provided for the compounds commensurate in scope of the claims and there is no disclosure regarding how the *in vitro* results correlate to *in vivo* tests.

6) The breadth of the claims: The instant claims embrace treating all diseases associated with modulation of chemokine receptor activity, etc., which diseases include inflammatory diseases, cancer, etc.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Habashita et al., WO 2001/040227. The instant claims read on reference disclosed compounds, see the structural formula (I) in page 1 and the corresponding species of the Examples. The compounds are disclosed to be useful as pharmaceutical therapeutic agents, see the abstract. (U.S. Patent No. 7,119,091 which issued from the national stage application corresponding to PCT/JP00/08517 is relied upon as English equivalent of WO document).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Habashita et al., WO 2001/040227 (US 7,119,091 issued from the corresponding national stage application relied upon as the English equivalent). The reference teaches a generic group of triazaspiro[5.5]undecane compounds, which embraces applicant's instantly claimed compounds. See formula (I) in page 1, and the corresponding species of the examples. The compounds are taught to be useful as pharmaceutical therapeutic agents, see the abstract. The instant claims differ from the reference by reciting specific species or a more limited subgenus than the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-10 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 7,119,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims substantially overlap the compounds of the reference claims, see the claims in each of the application. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the compounds from the reference claims and/or use the compounds in any of the methods taught by the reference, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to

select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

2. Claims 11-12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 7,285,552. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims substantially overlap the method of treatment of the reference claims, see the claims in each of the application. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the compounds from the reference claims and/or use the compounds in any of the methods taught by the reference, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

3. Claims 1-12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 10/555,611. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims substantially overlap the compounds of the reference claims, see the claims in each of the application. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the compounds from the reference claims and/or use the compounds in any of the methods taught by the reference, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any

of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-11, 22, 28-29 and 35-36 of copending Application No. 10/527,193 (now allowed). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims substantially overlap the compounds of the reference claims, see the claims in each of the application. It would have been obvious to one having ordinary skill in the art at the time of the invention to select the compounds from the reference claims, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Duplicate Claims

Applicant is advised that should claim 8 be found allowable, claims 9-10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two or more claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 9 and 10 recite an intended use for the composition of claim 8 and are therefore, not patentably distinct from the composition of claim 8.

Receipt is acknowledged of the Information Disclosure Statements filed on March 11, 2005 and July 20, 2007 and copies are enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

January 4, 2008